REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. EXAMINER INTERVIEW, CLAIM STATUS & AMENDMENTS

Applicants sincerely thank Examiner Hong for speaking with Applicants' representative on November 17, 2008. Both this conversation and the indication that the restriction requirement was a species election as shown in item 2 on page 2 of the Office Action are appreciated. It is Applicants' understanding based upon the above that if the elected species is found allowable then the search will be extended to the other species of the claimed invention.

Claims 1, 2, 4-13, 16, 17 and 20-31 were pending in this application when last examined.

Claims 1, 2, 4-13, 27, 28 and 30 were examined on the merits and stand rejected.

Claims 16, 17, 20-26, 29 and 31 were withdrawn as non-elected subject matter.

Applicants' reserve the right to file a continuation or divisional application on any non-elected subject matter.

Claims 7 and 27 are amended to clarify the claimed invention. Claim 1 is amended to correct an informality.

No new matter has been added.

I. CLAIM OBJECTIONS

In items 6 and 7 on page 3 of the Office Action, claims 7 and 27 were objected to. These objections are overcome, as applied to the amended claims, for reasons which are self-evident.

II. OBVIOUSNESS REJECTION

In item 9 on pages 4-9 of the Office Action, claims 1, 2, 4-13, 27, 28 and 30 were newly rejected under 35 U.S.C. § 103(a) as obvious over Chen in view of Rava et al., Klessing et al., Poethke et al., Hu and Sanderson et al. Applicants respectfully traverse this rejection.

Disclosure of Chen

The Examiner is correct that Chen describes "classic screening methods" for specific monoclonal antibodies (page 1 of the translation). Such classic screening methods are also shown in the left-hand panel of Figure 1 of Chen, described on page 4 of the translation. In these "classic screening methods", a mouse is immunized with a specific antigen, spleen cells from the mouse are isolated and used to produce hybridomas which are cloned. The monoclonal antibodies secreted by the hybridoma clones are individually screened using standard assays to identify clones producing antibodies that bind to the specific antigen. The authors of Chen consider such "classic screening methods" to be inefficient (page 2 of the translation, paragraph 1).

To improve the efficiency of these "classic screening methods", the authors in Chen disclose immunizing mice with homogenized tissue extracts. Cells from the immunized mice are used to create hybridoma cell lines and the supernatants of these hybridoma cell lines are printed onto a chip. The method in Chen thus involves printing monoclonal antibodies against antigens in the homogenized tissue extracts onto the chip. Specific antigens are passed over the chip in the hope that they will be bound by one or more of the monoclonal antibodies printed on the chip. In a separate step, polyclonal antibodies are raised to these specific antigens. Binding of an antigen to a monoclonal antibody on the chip is detected using an antigen-specific polyclonal antibody.

This method is described generically on page 2, paragraph 2 of the English translation of Chen and is shown in the right-hand panel of Figure 1 which is described on page 3 of the translation. The principle of the "protein chip" is described in more detail in Figures 2 and 3 of Chen. Figure 2 shows that, once the supernatants of the antibodies have been spotted to create the antibody chip, hybridoma clones that are producing mouse antibodies can be identified using anti-mouse antibodies. In order to identify an antibody that binds to a specific antigen, Chen incubates the spotted supernatants with an antigen and then with a polyclonal antibody binding to the bound antigen, as shown in Figure 3, described on page 4 of the translation.

- ***The claimed method differs from the disclosure of Chen and advantages are associated with those differences***

The method disclosed in Chen differs from the method claimed in the current application in that it involves immunization with homogenized tissue, rather than with a plurality of purified

candidate antigens. The method disclosed in Chen further differs from the methods claimed in that Chen involves identifying a monoclonal antibody against a particular antigen by spotting monoclonal antibodies onto a chip, adding the antigen and detecting the binding of the antigen to a monoclonal antibody using polyclonal antibodies produced in a separate step. The methods claimed identify monoclonal antibodies against specific antigens simply by adding the supernatants of monoclonal antibody-producing hybridoma cell lines directly to protein chips displaying the purified candidate antigens. Chen does not suggest either of these two features.

The method disclosed in Chen involves building a bank of hybridoma cell lines at random by immunization with homogenized tissue extracts. The supernatants of these hybridoma cell lines can be screened to identify a monoclonal antibody against a particular antigen of interest only after raising a corresponding polyclonal antibody against that antigen. This is a very laborious method since a polyclonal antibody must be raised against every antigen of interest before a monoclonal antibody can be identified. Furthermore, the polyclonal and monoclonal antibodies will sometimes compete for the same binding site on the antigen. If this occurs, the polyclonal antibody will not be able to bind the antigen already bound by the monoclonal antibody, leading to a failure to identify a monoclonal antibody that binds the antigen.

In contrast, the claimed methods allow the skilled person to build systematically a bank of hybridoma cell lines producing antibodies against pre-determined antigens. The animal is immunized with one or more purified candidate antigens against which it is desired to isolate monoclonal antibodies rather than with a homogenized tissue extract containing a random combination of antigens as disclosed in Chen. Cell lines producing monoclonal antibodies against the antigens with which the animal is immunized can be used to build a bank of hybridoma cell lines encompassing entire organismic proteomes. Monoclonal antibodies against specific antigens are identified by spotting supernatants from antibody-producing hybridoma cells onto a protein chip bearing the antigen. This is the opposite of Chen where the antigen is added to a chip bearing the monoclonal antibody and binding between the monoclonal antibody and the antigen is detected using a polyclonal antibody. Further, unlike the method in Chen, the methods of the invention do not run the risk of generating false negative results because there are no polyclonal antibodies to compete with the monoclonal antibodies for the antigen binding site.

The methods claimed thus display numerous advantages over the method disclosed in Chen, none of which are taught or suggested by Chen.

- ***There would have been no motivation to modify the method of Chen in view of Rava, Klessing, Poethke or Hu.***

Contrary to the Examiner's assertions, the teachings of Rava, Klessing, Poethke and Hu do not make up for the deficiencies in Chen nor do they render obvious the numerous advantages of the claimed methods over the method disclosed in Chen.

The Examiner argues that the skilled person would have been motivated to modify the method of Chen to use a protein chip coated with purified peptides instead of monoclonal antibodies in view of the teaching of Chen itself or of Rava. It is respectfully submitted this argument is incorrect. All of the discussion in Chen relates to chips displaying antibodies; there is no teaching in Chen of how to conduct methods using chips displaying antigens.

Rava relates to biological chip plates comprising a plurality of wells, each containing a biological array containing probes (column 2, first paragraph). According to column 3 of Rava, examples of probes "include but are not restricted to, agonist and antagonists for cell membrane receptors, toxins and venoms, viral epitopes, hormones (e.g. opioid peptides, steroids, etc.), hormone receptors, peptides, enzymes, enzyme substrates, cofactors, drugs, lectins, sugars, oligonucleotides, nucleic acids, oligosaccharides, proteins, and monoclonal antibodies". Rava thus teaches the existence of chips displaying peptides but only in the context of chips displaying a wide variety of additional probes. Rava does not provide the skilled person with any motivation to using consider chips displaying peptides in the method of Chen.

Furthermore, Applicants respectfully suggest that the Examiner is incorrect that "the claims would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention". Substituting the chips displaying antibodies in Chen for the chips displaying peptides mentioned in passing in Rava would not on its own have resulted in the method recited in the claims. Further modifications to the methods disclosed in Chen would have been required that were not obvious from either Chen or Rava. In particular, the method in Chen would have had to have been modified to allow detection of antibodies directly, rather than via an antigen and a

polyclonal antibody, something that is not suggested in Chen. It is these additional modifications to the method in Chen, in combination with the substitution of chips displaying antigens rather than antibodies, which result in the huge advantages discussed above that were not predictable to the skilled person from either document.

The Examiner argues that the skilled person would have been motivated to further modify the method of Chen to immunize the animals with purified peptides instead of homogenized tissue because of the teachings of Klessing, Poethke and Hu. These three documents merely suggest immunizing animals with a plurality of antigens. However, as the Examiner acknowledges, they do not provide any link to screening for antibodies against these antigens using chips displaying them. It would not therefore have been obvious to modify the method of Chen to employ purified antigens instead of homogenized tissue.

- ***Summary***

The obviousness rejection raised by the Examiner has been made with the benefit of hindsight and with knowledge of the current invention. The Examiner is picking and choosing features from several different documents and combining them with Chen in an attempt to arrive at the invention recited in claim 1. The Examiner has failed to take proper consideration of whether the skilled person would have been motivated to combine these documents and make the substitutions she considers would have led to the claimed methods. In fact, as discussed above, the use of purified candidate antigens and the use of antigen chips would not have been minor substitutions; making these changes would have required the skilled person to adopt a completely different mindset and make significant modifications to the method employed by Chen.

Enormous advantages are obtained by using the method of the invention in comparison with the laborious prior art methods for producing monoclonal antibodies in Chen, as discussed above. The advantages associated with the invention in terms of the ability to enable the high-throughput production and screening of monoclonal antibodies against large numbers of antigens simultaneously were further demonstrated by the Applicant in the publication by De Masi et al. (Proteomics, 2005, (16):4070-81) filed earlier in prosecution. It was of course hugely desirable in the prior art to achieve these advantages. However, none of the documents cited by the Examiner suggest that these advantages over the prior art could be achieved by significantly modifying the

method in Chen to develop a method for producing monoclonal antibodies involving immunization with purified antigens and identifying monoclonal antibodies using a protein chip displaying antigens. It might well have been obvious to the skilled person that it was desirable to achieve these advantages but it would not have been obvious how to achieve them. The claimed methods are therefore non-obvious and the above-noted is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

Alan M. SAWYER et al.

/William R. Schmidt, II/

Digitally signed by /William R. Schmidt, II/
DN: cn=/William R. Schmidt, II/, o=WLP, ou, email=bschmidt@wenderoth.com, c=US
Date: 2009.05.18 16:34:21 -04'00'

By: _____

William R. Schmidt, II
Registration No. 58,327
Attorney for Applicants

WRS/vah
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
May 18, 2009